I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on December 31, 2007.

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 AND UNDER 37 CFR 1.323
Docket No. G-078US04CIP
Patent No. 7,060,479

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert
Issued	:	June 13, 2006
Patent No.	:	7,060,479
For	:	Full-Length Human cDNAs Encoding Potentially Secreted Proteins

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)
UNDER 37 CFR 1.323 (APPLICANTS' MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Should Read:**
Column 2, line 1:	Page 2, line 8:
"ofter"	--often--
Column 12, line 61:	Page 14, line 27:
"60/187"	--60/187,470--

Patent Reads:	**Application Reads:**
Column 16, line 19:	Page 18, lines 20-21:
"96%, 96%, 98relative to"	--96%, 96%, 98%, 99%, or 100% pure relative to--
Patent Reads:	**Application Should Read:**
Column 22, line 18:	Page 25, line 9:
"Randomization Group25"	--Randomization Group 25,--
Column 32, line 61:	Page 37, line 23:
"present invention is a"	--present invention are a--
Patent Reads:	**Application Reads:**
Column 35, line 29:	Page 40, line 20:
"telomerc repeats"	--telomeric repeats--
Patent Reads:	**Application Should Read:**
Column 43, line 18:	Page 49, line 17:
"either fill-length"	--either full-length--
Patent Reads:	**Application Reads:**
Column 63, lines 35-36:	Page 72, line 17:
"$5x10^{-}{}_{15}M$"	--$5x10^{-15}M$--
Column 83, line 36:	Page 96, line 4:
"containing 25 ∞g/ml"	--containing 25 μg/ml--
Patent Reads:	**Application Should Read:**
Column 86, line 26:	Page 99, line 17:
"between 0,1 and"	--between 0.1 and--

Patent Reads:	**Application Reads:**
Column 95, line 37:	Page 110, line 2:
"groups firm"	--groups from--
Column 99, line 19:	Page 114, lines 8-9:
"contain domain"	--contain the LRR domain--
Patent Reads:	**Application Should Read:**
Column 102, line 9:	Page 117, line 17:
"chromatograpy"	--chromatography--
Column 103, line 5:	Page 118, line 18:
"binding domain domain"	--binding domain--
Column 103, line 24:	Page 118, lines 29-30:
"zinc fingers domains"	--zinc finger domains--
Column 107, line 49:	Page 123, line 20:
"shown to activates"	--shown to activate--
Column 108, line 10:	Page 123, line 36:
"exemple"	--example--
Column 108, line 44:	Page 124, line 19:
"immunohistochemisty"	--immunohistochemistry--
Patent Reads:	**Application Reads:**
Column 110, line 58:	Page 126, line 36:
"extramacrochactac"	--extramacrochaetae--

Patent Reads:	**Application Should Read:**
Column 113, line 55:	Page 130, line 13:
"invention havinf an"	--invention having an--
Column 127, lines 31-32:	Page 145, line 17:
"is caracterized by"	--is characterized by--
Column 127, line 52:	Page 145, line 29:
"plant epoxyde hydrolase"	--plant epoxide hydrolase--
Column 127, line 58:	Page 145, line 32:
"hydratation"	--hydration--
Column 128, line 11:	Page 146, line 8:
"may be associed with"	--may be associated with--
Column 128, line 35:	Page 146, line 22:
"an epoxyde hydrolase"	--an epoxide hydrolase--
Column 129, line 29:	Page 147, line 22:
"Biochemistry 29 1425-1435"	--Biochemistry 29:1425-1435--
Column 129, line 60:	Page 148, line 6:
"nutrient and gaz"	--nutrient and gas--
Column 130, line 26:	Page 148, line 27:
"deficient fonction"	--deficient function--
Column 131, line 38:	Page 150, line 1:
"that is the hallmarks"	--that is the hallmark--

Column 132, line 17:

"participate to regulation"

Page 150, line 30:

--participate in regulation--

Column 133, line 51:

"immunohistochemisty"

Page 152, line 16:

--immunohistochemistry--

Column 136, lines 65-66:

"and embryogenesis Individuals"

Page 155, line 37:

--and embryogenesis. Individuals--

Patent Reads:

Application Reads:

Column 140, line 54:

"alkali bums"

Page 160, line 11:

--alkali burns--

Column 143, line 10:

"treatment of bums"

Page 162, line 31:

--treatment of burns--

Column 143, line 13:

"healing of bums. The bums"

Page 162, line 33:

--healing of burns. The burns--

Column 143, line 17:

"there are bums"

Page 162, line 35:

--there are burns--

Column 143, line 18:

"contacting the bum"

Page 162, line 36:

--contacting the burn--

Patent Reads:

Application Should Read:

Column 146, line 25:

"thuman pancreatic"

Page 166, line 15:

--human pancreatic--

Column 149, lines 36-37:

"Kaun et Saier"

Page 169, line 33:

--Kaun and Saier--

Column 150, line 4:	Page 170, line 18:
"Kaun et Saier"	--Kaun and Saier--
Column 153, lines 34-35:	Page 174, line 21:
"composition and methods"	--compositions and methods--
Column 155, line 32:	Page 176, line 28:
"donnor"	--donor--
Column 156, line 37:	Page 177, line 36:
"celullar proteins"	--cellular proteins--
Column 157, line 62:	Page 179, line 17:
"fusosyltransferase"	--fucosyltransferase--
Column 159, line 5:	Page 180, line 27:
"model of"	--models of--
Column 159, line 11:	Page 180, line 31:
"fusosyltransferase"	--fucosyltransferase--
Patent Reads:	**Application Reads:**
Column 159, line 21:	Page 181, line 1:
"or pat thereof"	--or part thereof--
Patent Reads:	**Application Should Read:**
Column 159, line 55:	Page 180, line NEED A LINE NUMBER:
"related to"	--relates to--
Column 160, line 47:	Page 182, line 22:
"immunohistochemisty"	--immunohistochemistry--

Column 164, line 15:	Page 186, line 14:
"frаments thereof"	--fragments thereof--
Column 168, line 15:	Page 190, line 29:
"chromatograpy"	--chromatography--
Column 173, line 12:	Page 196, line 10:
"exemple"	--example--
Column 173, line 23:	Page 196, line 17:
"exemple"	--example--
Column 174, line 36:	Page 197, line 28:
"relulation"	--regulation--
Column 177, line 16:	Page 200, line 27:
"immunohistochemisty"	--immunohistochemistry--
Column 177, line 29:	Page 200, line 36:
"U.S. Pat. No. 552,277"	--U.S. Pat. No. 5,552,277--
Column 186, line 30:	Page 211, line 5:
"$p34^{SEI-}$ seems"	--$p34^{SEI-1}$ seems--
Column 191, line 6:	Page 216, lines 17-18:
"purified the protein"	--purified protein--
Column 192, line 51:	Page 218, lines 15-16:
"SEQ ID NO: HOPP"	--SEQ ID NO: 259--
Column 193, line 37:	Page 219, line 9:
"methods Kohler"	--methods of Kohler--

Patent Reads:	**Application Reads:**
Column 195, line 27:	Page 221, lines 14-15:
"clone 15 188-28-4-0-B12-CS"	--clone 188-28-4-0-B12-CS--
Column 198, line 59:	Page 225, line 7:
"to functions as"	--to function as--
Patent Reads:	**Application Should Read:**
Column 201, line 8:	Page 227, line 21:
"conserved cysteines residues"	--conserved cysteine residues--
Column 206, line 66:	Page 234, line 5:
"memebers"	--members--
Column 209, lines 31-32:	Page 236, line 33:
"metastatispreferably brain cancer"	--metastasis, preferably brain cancer--
Column 211, line 21:	Page 238, line 36:
"trought its"	--through its--
Column 212, line 49:	Page 240, line 18:
"eucaryote"	--eukaryote--
Column 212, line 54:	Page 240, line 21:
"procaryote"	--prokaryote--
Column 213, line 42:	Page 241, line 17:
"neuromuscularjunction"	--neuromuscular junction--
Column 217, line 29:	Page 245, line 30:
"marquer"	--marker--

Column 217, line 52:

"postherpetic"

Page 246, line 8:

--post-therapeutic--

Column 223, line 31:

"gliobastoma"

Page 252, line 19:

--glioblastoma--

Patent Reads:

Column 223, line 48:

"fragments thereof Further preferred"

Application Reads:

Page 252, line 30:

--fragments thereof. Further preferred--

Patent Reads:

Column 224, line 37:

"In further"

Application Should Read:

Page 253, line 27:

--In a further--

Column 225, line 1:

"in further"

Page 254, line 7:

--in a further--

Column 225, line 19:

"In further"

Page 254, line 18:

--In a further--

Column 226, line 6:

"gliobastoma"

Page 255, line 12:

--glioblastoma--

Column 226, line 19:

"gliobastoma"

Page 255, line 20:

--glioblastoma--

Patent Reads:

Column 234, lines 17-18:

"Golgi cistemae"

Application Reads:

Page 264, line 19:

--Golgi cisternae--

Patent Reads:	**Application Should Read:**
Column 237, line 62:	Page 268, line 17:
"gliobastoma"	--glioblastoma--
Column 239, line 1:	Page 269, line 25:
"In further"	--In a further--
Column 239, line 32:	Page 270, line 5:
"in further"	--in a further--
Column 239, line 50:	Page 270, line 16:
"In further"	--In a further--
Column 240, line 37:	Page 271, line 10:
"gliobastoma"	--glioblastoma--
Column 240, line 50:	Page 271, line 18:
"gliobastoma"	--glioblastoma--
Column 241, line 49:	Page 272, line 26:
"neurogenerative"	--neurodegenerative--
Column 241, line 60:	Page 272, line 33:
"provide methods"	--provides methods--
Column 242, lines 15-16:	Page 273, line 11:
"neurogenerative"	--neurodegenerative--
Column 242, lines 64-65:	Page 274, line 3:
"neurogenerative"	--neurodegenerative--

Column 244, line 61:	Page 276, line 8:
"int the"	--in the--
Column 246, line 3:	Page 277, line 17:
"Cterminal"	--C terminal--
Column 249, line 10:	Page 280, line 32:
"Pancreas :139-149"	--Pancreas 9(2):139-149--
Column 251, line 4:	Page 282, line 36:
"chromatograpy"	--chromatography--
Column 251, line 4:	Page 282, line 36:
"prepartation"	--preparation--
Column 251, line 57:	Page 283, line 33:
"(1993"	--(1993)--
Column 257, line 66:	Page 290, line 28:
"In further"	--In a further--
Column 258, line 9:	Page 290, line 35:
"In further"	--In a further--
Column 258, line 23:	Page 291, line 7:
"In further"	--In a further--
Column 260, line 6:	Page 293, line 22:
"In further"	--In a further--
Column 260, line 9:	Page 293, line 24:
"In further"	--In a further--

Column 263, line 4:	Page 296, line 34:
"diarrhoea"	--diarrhea--
Column 265, line 15:	Page 299, line 13:
"CO2 hydration"	--CO_2 hydration--
Column 265, line 26:	Page 299, line 20:
"CO2 hydration"	--CO_2 hydration--
Column 267, line 53:	Page 302, line 9:
"chromatograpy"	--chromatography--
Column 268, line 52:	Page 303, line 15:
"doamins"	--domains--
Column 275, line 4:	Page 310, line 16:
"frombrain"	--from brain--
Column 275, line 28:	Page 310, line 30:
"chromatograpy"	--chromatography--
Column 281, line 22:	Page 317, line 16:
"chromatograpy"	--chromatography--
Column 281, line 23:	Page 317, line 17:
"prepartation"	--preparation--
Column 281, line 65:	Page 318, line 7:
"exon2"	--exon 2--
Column 282, line 3:	Page 318, line 10:
"intron1"	--intron 1--

Column 282, line 20:	Page 318, line 19:
"differenctiation"	--differentiation--
Column 282, line 44:	Page 318, line 33:
"Some throughly studied"	--Some thoroughly studied--
Column 282, line 47:	Page 318, line 34:
"et Al reported"	--et al. reported--
Column 283, line 61:	Page 320, line 11:
"chromatograpy"	--chromatography--
Column 283, line 61:	Page 320, line 12:
"prepartation"	--preparation--
Patent Reads:	**Application Reads:**
Column 292, line 29:	Page 329, line 37:
"bum healing"	--burn healing--
Patent Reads:	**Application Should Read:**
Column 293, line 21:	Page 331, line 4:
"polypeptidehas"	--polypeptide has--
Column 294, line 63:	Page 332, line 36:
"demntia"	--dementia--
Patent Reads:	**Application Reads:**
Column 295, line 61:	Page 334, line 5:
"comichon"	--cornichon--

Patent Reads:	**Application Should Read:**
Column 297, line 32:	Page 335, line 35:
"demntia"	--dementia--
Column 300, line 26:	Page 339, line 11:
"twomembrane-spanning"	--two membrane-spanning--
Column 303, line 41:	Page 342, line 34:
"particulary"	--particularly--
Column 304, line 61:	Page 344, line 14:
"svere"	--severe--
Patent Reads:	**Application Reads:**
Column 309, line 34:	Page 349, line 13:
"Croh's disease"	--Crohn's disease--
Patent Reads:	**Application Should Read:**
Column 314, line 45:	Page 355, line 2:
"enzymes labels"	--enzyme labels--
Patent Reads:	**Application Reads:**
Column 322, line 10:	Page 363, line 14:
"Protiens of"	--Protein of--
Patent Reads:	**Application Should Read:**
Column 324, line 12:	Page 365, line 22:
"embodiment, The"	--embodiment, the--
Column 336, line 4:	Page 378, line 32:
"specifically bine the"	--specifically bind the--

Column 342, line 48:	Page 386, line 13:
"potasssium"	--potassium--
Column 347, line 66:	Page 392, line 20:
"specifically binds a"	--specifically bind a--
Column 351, line 25:	Page 396, line 17:
"compartments/organelels"	--compartments/organelles--
Column 353, line 28:	Page 398, line 34:
"(e.g. biopsies."	--(e.g. biopsies).--
Column 355, line 13:	Page 401, line 3:
"Diphteria toxin A"	--Diphtheria toxin A--
Column 367, line 12:	Page 414, line 32:
"biological activty"	--biological activity--
Column 372, line 35:	Page 421, line 5:
"titaniumdioxide"	--titanium dioxide--
Patent Reads:	**Application Reads:**
Column 376, line 2:	Page 425, line 5:
"manipule"	--manipulate--
Column 394, lines 47-48:	Page 446, line 4:
"Muller et al. I Eur. J."	--Muller et al. Eur. J.--
Column 433, Table Vb, SEQ ID NO:166:	Page 492, Table Vb, SEQ ID NO: 166:
"1-1];"	--[1-1];--.

A true and correct copy of pages 18, 40, 72, 96, 110, 114, 126, 160, 162, 181, 221, 225, 252, 264, 329, 334, 349, 363, 425, 446, and 492 of the specification as filed which support Applicants' assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

The fee of $100.00 was paid at the time this Request was filed. The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/dc/sl

Attachments: Copy of pages 18, 40, 72, 96, 110, 114, 126, 160, 162, 181, 221, 225, 252, 264, 329, 334, 349, 363, 425, 446, and 492 of the specification

RNA and subsequently isolating individual clones from that library results in an approximately 10^4-10^6 fold purification of the native message.

The term "purified" is further used herein to describe a polypeptide or polynucleotide of the invention which has been separated from other compounds including, but not limited to, polypeptides or polynucleotides, carbohydrates, lipids, etc. The term "purified" may be used to specify the separation of monomeric polypeptides of the invention from oligomeric forms such as homo- or hetero- dimers, trimers, etc. The term "purified" may also be used to specify the separation of covalently closed polynucleotides from linear polynucleotides. A polynucleotide is substantially pure when at least about 50%, preferably 60 to 75% of a sample exhibits a single polynucleotide sequence and conformation (linear versus covalently close). A substantially pure polypeptide or polynucleotide typically comprises about 50%, preferably 60 to 90% weight/weight of a polypeptide or polynucleotide sample, respectively, more usually about 95%, and preferably is over about 99% pure. Polypeptide and polynucleotide purity, or homogeneity, is indicated by a number of means well known in the art, such as agarose or polyacrylamide gel electrophoresis of a sample, followed by visualizing a single band upon staining the gel. For certain purposes higher resolution can be provided by using HPLC or other means well known in the art. As an alternative embodiment, purification of the polypeptides and polynucleotides of the present invention may be expressed as "at least" a percent purity relative to heterologous polypeptides and polynucleotides (DNA, RNA or both). As a preferred embodiment, the polypeptides and polynucleotides of the present invention are at least; 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 96%, 98%, 99%, or 100% pure relative to heterologous polypeptides and polynucleotides, respectively. As a further preferred embodiment the polypeptides and polynucleotides have a purity ranging from any number, to the thousandth position, between 90% and 100% (e.g., a polypeptide or polynucleotide at least 99.995% pure) relative to either heterologous polypeptides or polynucleotides, respectively, or as a weight/weight ratio relative to all compounds and molecules other than those existing in the carrier. Each number representing a percent purity, to the thousandth position, may be claimed as individual species of purity.

As used interchangeably herein, the terms "nucleic acid molecule(s)", "oligonucleotide(s)", and "polynucleotide(s)" include RNA or DNA (either single or double stranded, coding, complementary or antisense), or RNA/DNA hybrid sequences of more than one nucleotide in either single chain or duplex form (although each of the above species may be particularly specified). The term "nucleotide" is used herein as an adjective to describe molecules comprising RNA, DNA, or RNA/DNA hybrid sequences of any length in single-stranded or duplex form. More precisely, the expression "nucleotide sequence" encompasses the nucleic material itself and is thus not restricted to the sequence information (i.e. the succession of letters chosen among the four base letters) that biochemically characterizes a specific DNA or RNA molecule. The term "nucleotide" is also used herein as a noun to refer to individual nucleotides or varieties of nucleotides, meaning a molecule, or

nucleotide position that a polynucleotide fragment of the present invention, at least 8 contiguous nucleotides in length, could occupy on a polynucleotide of the invention is included in the invention as an individual species. The polynucleotide fragments specified by 5' and 3' positions can be immediately envisaged and are therefore not individually listed solely for the purpose of not unnecessarily lengthening the specifications.

It is noted that the above species of polynucleotide fragments of the present invention may alternatively be described by the formula "a to b"; where "a" equals the 5' most nucleotide position and "b" equals the 3' most nucleotide position of the polynucleotide; and further where "a" equals an integer between 1 and the number of nucleotides of the polynucleotide sequence of the present invention minus 8, and where "b" equals an integer between 9 and the number of nucleotides of the polynucleotide sequence of the present invention; and where "a" is an integer smaller then "b" by at least 8.

The present invention also provides for the exclusion of any species of polynucleotide fragments of the present invention specified by 5' and 3' positions or sub-genuses of polynucleotides specified by size in nucleotides as described above. Any number of fragments specified by 5' and 3' positions or by size in nucleotides, as described above, may be excluded. Specifically excluded from the invention are the fragments described in Table IV. For these cDNAs referred to by their sequence identification numbers, Table IV gives the positions of excluded fragments within these sequences fragments having substantial homology to polyadenylation tails and to repeated sequences including Alu, L1, THE and MER repeats, SSTR sequences or satellite, micro-satellite, and telomeric repeats. Each fragment is represented by a-b where a and b are the start and end positions respectively of a given excluded fragment. Excluded fragments are separated from each other by a coma. As used herein the term "polynucleotide described in Table IV" refers to all polynucleotide fragments defined in Table IV in this manner.

Preferred included and excluded polynucleotide fragments of the invention are also described in Tables Va and Table Vb. For these cDNAs referred to by their sequence identification numbers, Tables Va and Table Vb give the positions of preferred fragments within these sequences (columns entitled "Preferentially included fragments") as well as the positions of preferentially excluded fragments (columns entitled "Preferentially excluded fragments"). Each fragment is represented by a-b where a and b are the start and end positions respectively of a given preferred fragment. Fragments are separated from each other by a coma. As used herein the term "excluded polynucleotide described in Tables Va and Vb" refers to all polynucleotide preferentially excluded as described in Tables Va and Vb. As used herein the term "preferred polynucleotide described in Tables Va and Vb" refers to all preferrentially included polynucleotide fragments listed in Tables Va and Table Vb in this manner.

Therefore, the present invention encompasses isolated, purified, or recombinant polynucleotides which consist of, consist essentially of, or comprise a contiguous span of at least 8, 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, 500, 1000 or 2000 nucleotides

polypeptide comprising at least 6 consecutive amino acids, preferably at least 8 to 10 consecutive amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 consecutive amino acids of a sequence selected from the group consisting of SEQ ID Nos: 242-482 and sequences of the clone inserts of the deposited clone pool.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not specifically bind any other analog, ortholog, or homologue of the polypeptides of the present invention are included. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein, e.g., using FASTDB and the parameters set forth herein) to a polypeptide of the present invention are also included in the present invention. Further included in the present invention are antibodies, which only bind polypeptides encoded by polynucleotides, which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity. Preferred binding affinities include those with a dissociation constant or Kd less than $5X10^{-6}M$, $10^{-6}M$, $5X10^{-7}M$, $10^{-7}M$, $5X10^{-8}M$, $10^{-8}M$, $5X10^{-9}M$, $10^{-9}M$, $5X10^{-10}M$, $10^{-10}M$, $5X10^{-11}M$, $10^{-11}M$, $5X10^{-12}M$, $10^{-12}M$, $5X10^{-13}M$, $10^{-13}M$, $5X10^{-14}M$, $10^{-14}M$, $5X10^{-15}M$, and $10^{-15}M$.

The invention also concerns a purified or isolated antibody capable of specifically binding to a mutated GENSET protein or to a fragment or variant thereof comprising an epitope of the mutated GENSET protein.

Preparation of antibodies

The antibodies of the present invention may be prepared by any suitable method known in the art. Some of these methods are described in more detail in the example entitled "Preparation of Antibody Compositions to ". For example, a polypeptide of the present invention or an antigenic fragment thereof can be administered to an animal in order to induce the production of sera containing "polyclonal antibodies". As used herein, the term "monoclonal antibody" is not limited to antibodies produced through hybridoma technology but it rather refers to an antibody that is derived from a single clone, including eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technology.

Hybridoma techniques include those known in the art (*See, e.g.,* Harlow *et al.* 1988; Hammerling, *et al*, 1981). (Said references incorporated by reference in their entireties). Fab and F(ab')2 fragments may be produced, for example, from hybridoma-produced antibodies by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments).

incorporated by reference in its entirety. To generate P1 DNA for transgenic experiments, a preferred protocol is the protocol described by McCormick *et al.* (1994), which disclosure is hereby incorporated by reference in its entirety. Briefly, *E. coli* (preferably strain NS3529) harboring the P1 plasmid are grown overnight in a suitable broth medium containing 25 µg/ml of kanamycin. The P1 DNA is prepared from the *E. coli* by alkaline lysis using the Qiagen Plasmid Maxi kit (Qiagen, Chatsworth, CA, USA), according to the manufacturer's instructions. The P1 DNA is purified from the bacterial lysate on two Qiagen-tip 500 columns, using the washing and elution buffers contained in the kit. A phenol/chloroform extraction is then performed before precipitating the DNA with 70% ethanol. After solubilizing the DNA in TE (10 mM Tris-HCl, pH 7.4, 1 mM EDTA), the concentration of the DNA is assessed by spectrophotometry.

When the goal is to express a P1 clone comprising GENSET nucleotide sequences in a transgenic animal, typically in transgenic mice, it is desirable to remove vector sequences from the P1 DNA fragment, for example by cleaving the P1 DNA at rare-cutting sites within the P1 polylinker (*Sfi*I, *Not*I or *Sal*I). The P1 insert is then purified from vector sequences on a pulsed-field agarose gel, using methods similar to those originally reported for the isolation of DNA from YACs (*See e. g.*, Schedl *et al.*, 1993a; Peterson *et al.*, 1993), which disclosures are hereby incorporated by reference in their entireties. At this stage, the resulting purified insert DNA can be concentrated, if necessary, on a Millipore Ultrafree-MC Filter Unit (Millipore, Bedford, MA, USA – 30,000 molecular weight limit) and then dialyzed against microinjection buffer (10 mM Tris-HCl, pH 7.4; 250 µM EDTA) containing 100 mM NaCl, 30 µM spermine, 70 µM spermidine on a microdyalisis membrane (type VS, 0.025 µM from Millipore). The intactness of the purified P1 DNA insert is assessed by electrophoresis on 1% agarose (Sea Kem GTG; FMC Bio-products) pulse-field gel and staining with ethidium bromide.

Viral vectors

In one specific embodiment, the vector is derived from an adenovirus. Preferred adenovirus vectors according to the invention are those described by Feldman and Steg (1996), or Ohno *et al.*, (1994), which disclosures are hereby incorporated by reference in their entireties. Another preferred recombinant adenovirus according to this specific embodiment of the present invention is the human adenovirus type 2 or 5 (Ad 2 or Ad 5) or an adenovirus of animal origin (French patent application No. FR-93.05954), which disclosure is hereby incorporated by reference in its entirety.

Retrovirus vectors and adeno-associated virus vectors are generally understood to be the recombinant gene delivery systems of choice for the transfer of exogenous polynucleotides *in vivo* , particularly to mammals, including humans. These vectors provide efficient delivery of genes into cells, and the transferred nucleic acids are stably integrated into the chromosomal DNA of the host. Particularly preferred retroviruses for the preparation or construction of retroviral *in vitro* or *in vitro* gene delivery vehicles of the present invention include retroviruses selected from the group consisting of Mink-Cell Focus Inducing Virus, Murine Sarcoma Virus, Reticuloendotheliosis virus and Rous

Palmitoyl-protein thioesterase-1 (PPT1) is a lysosomal hydrolase that removes long-chain fatty acyl groups from modified cysteine residues in proteins. Mutations in PPT1 have been found to cause the infantile form of neuronal ceroid lipofuscinosis (INCL).

Soyombo and Hofmann (J. Biol. Chem. 272: 27456-27463 [1997]) identified cDNAs encoding PPT2. The deduced PPT2 protein contains 302 amino acids, including a 27-amino acid leader peptide, a sequence motif characteristic of many thioesterases and lipases, and 5 potential N-linked glycosylation sites. PPT2 shares 18% amino acid identity with PPT1. Soyombo and Hofmann tentatively localized the human PPT2 gene to 6p21.3. Northern blot analysis detected a predominant 2.0-kb PPT2 transcript in the human tissues examined, with the highest expression in skeletal muscle; variable amounts of 2.8- and 7.0-kb transcripts were also observed.

Cell fractionation studies indicate that PPT2 is present in the lysosomal fraction. Immunoblot analysis of recombinant PPT2 expressed in mammalian cells showed 6 PPT2 proteins ranging in size from 31 to 42 kDa. Treatment that removes asparagine-linked oligosaccharides resulted in a single major protein of 31 kDa and a minor protein of 33 kDa.

Recombinant PPT2, like PPT1, possesses thioesterase activity and localizes to the lysosome. Since PPT2 could not substitute for PPT1 in correcting the metabolic defect in INCL cells and was unable to remove palmitate groups from palmitoylated proteins, it appears that PPT2 possesses a different substrate specificity than PPT1. Another study, however, was able to show, after expression of the recombinant protein in a baculovirus system and using cell lysate as substrate, that the protein had S-thioesterase activity with a preference for acyl groups palmitic and myristic acid.

The subject invention provides the protein/polypeptide of SEQ ID NO:314, encoded by the cDNA of SEQ ID NO:73. The invention also provides biologically active fragments of SEQ ID NO:314. In one embodiment, the polypeptides of SEQ ID NO:314 are interchanged with the corresponding polypeptide encoded by the human cDNA of clone 188-41-1-0-B8-CS. "Biologically active fragments" are defined as those peptide or polypeptide fragments having at least one of the biological functions of the full length protein (e.g., removal of long-chain fatty acyl groups from modified cysteine residues in proteins). Compositions of the protein/polypeptide of SEQ ID NO:314, or biologically active fragments thereof, are also provided by the subject invention. These compositions may be made according to methods well known in the art.

The invention also provides variants of the protein of SEQ ID NO:314. These variants have at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the amino acid sequence encoded by SEQ ID NO:73. Variants according to the subject invention also have at least one functional or structural characteristic of the protein of SEQ ID NO:314. The invention also provides biologically active fragments of the variant proteins. Compositions of variants, or biologically active fragments thereof, are also provided by the subject invention. These compositions may be made according to methods well known in the art. Unless otherwise indicated, the methods disclosed herein can be practiced utilizing the protein encoded by

are highly homologous to the first 279 amino acids of the LGI1 (Leucine-rich gene – Glioma Inactivated) protein. Clones 188-11-1-0-B3-CS and 187-34-0-0-112-CS appear to be splicing and polymorphic variants of LGI1. The LGI1 protein is 557 amino acid in length. (See Somerville et al., (2000) Mammalian Genome 11, 622-627 ; Chernova, et al. (1998) Oncogene 17, 2873-2881, the disclosures of which are incorporated herein by reference in their entireties). Clone 188-11-1-0-B3-CS align with the first 279 amino acids of LGI1, followed by the addition of 12 amino acids (VLREIHRFTNMS) to the C-terminal end which do not appear to be homologous to LGI1. Like LGI1, clone 188-11-1-0-B3-CS and the polymorphic variant 187-34-0-0-112-CS contain the LRR domain and are highly expressed in brain tissue.

LGI1 belongs to a large family of leucine-rich repeat (LRR) proteins. It is believed that the LRR domains act as a region of protein-protein interaction. This has been substantiated as the family of known LRR proteins has grown. Leucine–rich repeats have been identified as essential components in glycoprotein hormone receptors, proteoglycans and the Trk proteins by expression of mutants and artificial chimaeras in tissue culture and by biochemical analysis of the properties of these constructs. Many transmembrane LRR proteins are known or suspected to encode truncated forms (N and L^6, and slit for example) with functional significance. The proteoglycan Decorin, a secreted protein, binds TGF-β, a growth factor which stimulates decorin expression. Since decorin inhibits growth of cultured cells, it may form part of a negative feedback loop to regulate cell growth. This is similar to the proposed function of the LGI1 receptor protein.

Analysis of brain gliomas has revealed that LGI1 expression is either abolished or greatly reduced in high-grade tumors compared with more benign ones, indicating a role as a tumor suppressor gene (Cowell et al. 2000; Cowell et al. 1998, the disclosure of which is incorporated herein by reference in its entirety). Most glioblastoma multiforme (GBM) brain tumors contain only one genomic copy of LGI1, and this one is almost invariably not expressed. How the gene is inactivated is not clear, although one possibility is that chromosome or gene rearrangement, which occur in 20-25% of tumors, cause inactivation as a result of a positional effect. Recently it was determined that the LGI1 gene is located on 10q24, and is disrupted by translocation in the T98G GBM cell line and is also rearranged in over 26% of primary brain tumors. Alternatively, LGI1 may be part of a highly regulated pathway where inactivation of other key members or high specific transcription factors results in either inactivation of all genes in the pathway or a failure to initiate transcription.

Since functional inactivation of LGI1 occurs during the transition of low-grade to high-grade brain tumors, knockout or transgenic mice in which the expression of the protein of SEQ ID NO:309 or 304 has been reduced, eliminated or altered may be used as disease model. In particular, mice that overexpress LGI1 may be used as a tumorigenesis model.

Mice are particularly useful as models for assessing the consequences of altering the level or activity of the proteins of SEQ ID NO:309 or 304 or to identify agents useful in treaating tumorigenesis, since human and mouse LGI1 are highly conserved, showing 91% identity at the

hydrophobic residues at every third and fourth position, and each helix contains several conserved residues (Murre C et al. (1989) Cell, 56:777-783; Benezra R. et al. (1990) Cell, 61:49-59).

The HLH protein family is subdivided into two major groups: the so-called "bHLH" and "non basic HLH" subfamilies. Proteins of the bHLH family contain a conserved highly basic region immediately N-terminal to the first helix (known as bHLH structure), and mutagenesis experiments on MyoD protein confirm that this region is responsible for sequence-specific binding to the "E-box", a consensus DNA motif for bHLH proteins (Davis RL. et al. (1990) Cell, 60: 733-746). A dimeric bHLH protein (either homodimeric or heterodimeric but in which both subunits contains a basic region) are able to bind to DNA. In general, the bHLH proteins fall into two categories: Class A consists of proteins that are ubiquitously expressed, including mammalian E12/E47 and fly da whereas the class B consists of proteins that are expressed in a more tissue-specific manner, including mammalian MyoD and fly AC-S. In most cases, the tissue-specific bHLH proteins preferentially heterodimerize with ubiquitous partners.

The non basic HLH subfamily contains proteins lacking a basic region unable to bind to DNA but that could form homo- or heterodimers through their HLH motif. Indeed, heterodimeric complexes between non basic HLH and bHLH proteins fail to bind to DNA and negatively modulate the bHLH proteins-mediated transcription activation. This phenomenon was first demonstrated in a MyoD/Id regulation model (Benezra R. et al. (1990) Cell, 61:49-59). The MyoD gene product is able to activate previously silent muscle-specific genes when introduced into a large variety of differentiated cell types. MyoD proteins form either homodimers or heterodimers with other bHLH proteins such as E12 or E47, and bind to E-box consensus motif to activate myogenesis. The Id gene, conserved from batracians to mammals (Wilson R et al. (1995) Mech.Dev. 49:211-222; Sawai S et al. (1997) Mech.Dev. 65:175-185; Norton JD et al. (1998) trends in Cell Biology 8:58-65), lacks a basic region adjacent to its HLH motif but is able to specifically dimerize with either MyoD, E12 or E14 and has been shown to subsequently attenuate the heterodimer's ability to bind DNA. Additionally, overexpression of Id inhibits MyoD-dependent gene activation in in vivo transfection experiments. Id proteins may function either to repress directly the activity of tissue-restricted bHLH proteins by rendering them non-functional or, more likely, to sequestrate the ubiquitous bHLH proteins and preventing them from forming active heterodimers with the tissue-restricted bHLH (Review by Norton JD et al. (1998) trends in Cell biology 8:58-65).

The possibility that the Id protein behaves as a dominant-negative regulator to repress MyoD protein activity through the formation of nonfunctional heterodimeric complexes is considerably strengthened by the following findings in Drosophila. In Drosophila, the development of peripheral nervous system is positively regulated by the two structurally related bHLH proteins, AS-C and daughterless (da), since loss of either activity results in loss of sensory organ development. The extramacrochaetae Emc product belonging to the non basic HLH subfamily was shown to antagonize

mediated glomerulonephritis such as the anti-Thy 1.1 rat model (Bagchus W. M., et al., Lab. Invest., 1986; 55:680-687; Lovett D. H., et al., Am. J. Pathol., 1992; 141:85-98).

In another embodiment, the protein of the invention is used in methods of treating inflamed or diseased gingiva comprising contacting the gingival with an efficient amount of MAMI polypeptides. Preferably, the MAMI polypeptide is delivered as a mouthwash or lavage or in a gell form. Collagenase and stromelysin activities have been demonstrated in fibroblasts isolated from inflamed gingiva (Uitto V. J., et al., J. Periodontal Res., 1981; 16:417-424), and enzyme levels have been correlated to the severity of gum disease (Overall C. M., et al., J. Periodontal Res., 1987; 22:81-88).

In another embodiment, the protein of the invention is useful for treating or detecting ulcers. Proteolytic degradation of extracellular matrix has been observed in corneal ulceration following alkali burns (Brown S. I., et al., Arch. Opthalmol., 1969;81:370-373). Thiol-containing peptides inhibit the collagenase isolated from alkali-burned rabbit corneas (Burns F. R., et al., Invest. Opththamol., 1989;30:1569-1575). Stromelysin, a member of the MMP family, is produced by basal keratinocytes in a variety of chronic ulcers (Saarialho-Kere U. K., et al., J. Clin. Invest., 1994;94:79-88). Stromelysin-1 mRNA and protein were detected in basal keratinocytes adjacent to but distal from the wound edge in what probably represents the sites of proliferating epidermis. Stromelysin-1 may thus prevent the epidermis from healing. MAMI may be used to inhibit Stromelysin-1, thereby enhance healing or decrease healing time.

In another embodiment, the protein of the invention can be used to inhibit angiogenesis, preferably tumor angiogenesis. This activity can be assayed in models of tumor angiogenesis (Taraboletti G., et al., Journal of the National Cancer Institute, 1995; 87:293; and Benelli R., et al., Oncology Research, 1994; 6:251-257). Davies et al., (Cancer Res., 1993; 53:2087-2091) reported that a peptide decreased the tumor burden and prolonged the survival of mice bearing human ovarian carcinoma xenografts. A peptide of the conserved MMP propeptide sequence was a weak inhibitor of gelatinase A and inhibited human tumor cell invasion through a layer of reconstituted basement membrane (Melchiori A., et al., Cancer Res., 1992; 52:2353-2356), and the natural tissue inhibitor of metalloproteinase-2 (TIMP-2) also showed blockage of tumor cell invasion in in vitro models (DeClerck Y. A., et al., Cancer Res., 1992; 52:701-708). Studies of human cancers have shown that gelatinase A is activated on the invasive tumor cell surface (Strongin A. Y., et al., J. Biol. Chem., 1993; 268:14033-14039) and is retained there through interaction with a receptor-like molecule (Monsky W. L, et al., Cancer Res., 1993; 53:3159-3164). Tumor angiogenesis, preferably sarcomas and carcinomas, may be inhibited by contacting tumor cells with an effective amount of a MAMI polypeptide. When used to inhibit tumor cells in vivo, the MAMI polypeptides are preferably delivered i.v. in an effective to inhibit tumor angiogenesis.

In another embodiment, the MAMI proteins of the invention can be used to treat and diagnose rheumatoid arthritis. Collagenases have been implicated in a number of diseases, including, rheumatoid arthritis (Mullins, D. E. et al 1983), and it has been proposed to use MMP inhibitors in the

The present invention also provides the use of an MMP inhibitor in the treatment or prophylaxis of a natural or artificial tissue comprising extracellular matrix components to inhibit, i.e. restrict, hinder or prevent, contraction of the tissue, especially contraction resulting from a pathological condition or from surgical or cosmetic treatment.

Cosmetic treatments, such as chemical or physical dermal abrasion, used as anti-ageing treatments, cause trauma to the skin. Use of MMP inhibitors, such as a MAMI polypeptide, during the healing process which occurs after the initial abrasion is a cosmetic use of MMP inhibitors according to the present invention.

The present invention also provides the use of an MMP inhibitor to inhibit, i.e. restrict, hinder or prevent, invasion by cells, especially fibroblasts, into tissue comprising an extracellular matrix and/or migration by cells, especially fibroblasts, in or through tissue comprising an extracellular matrix. The method comprises the step of contacting the fibroblasts or extracellular matrix with MMP inhibitors, preferably a MAMI polypeptide in an effective amount.

In another embodiment, the present protein is used to prevent or reduce contracture of scar tissue resulting from eye surgery. Glaucoma surgery to create new drainage channels often fails due to scarring and contraction of tissues. A method of preventing contraction of scar tissue formed in the eye, such as the application of a suitable agent, is therefore invaluable. Such an agent may also be used in the control of the contraction of scar tissue formed after corneal trauma or corneal surgery, for example laser or surgical treatment for myopia or refractive error in which contraction of tissues may lead to inaccurate results. It is also useful in cases where scar tissue is formed on/in the vitreous humor or the retina, for example, that which eventually causes blindness in some diabetics and that which is formed after detachment surgery, called proliferative vitreoretinopathy. Other uses include where scar tissue is formed in the orbit or on eye and eyelid muscles after squint, orbital or eyelid surgery, or thyroid eye disease and where scarring of the conjunctiva occurs as may happen after glaucoma surgery or in cicatricial disease, inflammatory disease, for example, pemphigoid, or infective disease, for example, trachoma. A further eye problem associated with the contraction of collagen-comprising tissues for which the methods and medicaments of the present invention may be used is the opacification and contracture of the lens capsule after cataract extraction. These methods comprise the step of contacting the affected part of the eye with an effective amount of a MAMI polypeptide.

In a preferred embodiment, the protein of the invention can be used for the treatment of burns. Contraction of collagen-comprising tissue, which may also comprise other extracellular matrix components, frequently occurs in the healing of burns. The burns may be chemical, thermal or radiation burns and may be of the eye, the surface of the skin or the skin and the underlying tissues. It may also be the case that there are burns on internal tissues, for example, caused by radiation treatment. These methods comprise the step of contacting the burn with an effective amount of a MAMI polypeptide.

activity of the protein of the invention or part thereof may be assayed using any of the assays known to those skilled in the art including those described in (Palcic et al. Carbohydr Res 1990; 196:133-40).

Fucosylated compounds have considerable potential both as therapeutics and as reagents for clinical assays. However, synthesis of glycosylated compounds of potential commercial and/or therapeutic interest is difficult because of the very nature of the saccharide subunits. A multitude of positional isomers in which different substituent groups on the sugars become involved in bond formation, along with the potential formation of different anomeric forms, are possible. As a result of these problems, large scale chemical synthesis of most carbohydrates is not possible due to economic considerations arising from the poor yields of desired products. Enzymatic synthesis using glycosyl transferases such as fucosyltransferase provides an alternative to chemical synthesis of carbohydrates. Enzymatic synthesis using glycosidases, glycosyl transferases, or combinations thereof, have been considered as a possible approach to the synthesis of carbohydrates. As a matter of fact, enzyme-mediated catalytic synthesis would offer dramatic advantages over the classical synthetic organic pathways, producing very high yields of carbohydrates economically, under mild conditions in aqueous solutions, and without generating notable amounts of undesired side products. To date, such enzymes are however difficult to isolate, especially from eukaryotic, e.g., mammalian sources, because these proteins are only found in low concentrations, and tend to be membrane-bound. In addition to being difficult to isolate, the acceptor (peptide) specificity of glycosyl transferases is poorly understood. Thus, there is a need for obtaining recombinant glycosyl transferase, including fucosyltransferases, that could be produced in very large amounts.

Thus, the invention related to methods and compositions using the protein of the invention or part thereof to synthesize glycosylated compounds, either glycoproteins, glycolipids, or oligosaccharides, more particularly fucosylated compounds. If necessary, the protein of the invention or part thereof may be produced in a soluble form by removing its transmembrane domains and/or its Golgi retention signal using any of the methods skilled in the art including those described in US patent 5,776,772. For example, the protein of the invention or part thereof is added to a sample containing GDP-fucose and a substrate compound in conditions allowing glycosylation, more particularly fucosylation and allowed to catalyze the glycosylation of this compound. In a preferred embodiment, the enzymatic reaction carried out by the protein of the invention is part of a series of other chemical and/or enzymatic reactions aiming at the synthesis of complex glycosylated compounds, such as the ones described in US patents 5,409,817 and 5,374,541. In another preferred embodiment where the method is to be practiced on a commercial scale, it may be advantageous to immobilize the glycosyltransferase on a support. This immobilization facilitates the removal of the enzyme from the batch of product and subsequent reuse of the enzyme. Immobilization of glycosyltransferases can be accomplished, for example, by removing from the transferase its membrane-binding domain, and attaching in its place a cellulose-binding domain. One of skill in the

Another protein of the Nol1/Nop2/Sun family, Nop2p, coded by the gene NOP2, has a role in nucleolar function during the onset of growth and in the maintenance of nucleolar structure (de Beus et al. (1994) J. Cell Biol. 127:1799-813). The two proteins, p120 and Nop2p, are associated to ribosomal RNA in pre-ribosomal particles and can mediate the maturation process of the ribosome (Hong B. et al. (1997) Mol. Cell Biol. 17:378-88; Gustafson W.C. et al. (1998) Biochem. J. 331:387-93).

The subject invention provides the polypeptides encoded by the human cDNA of clone 188-28-4-0-B12-CS and polynucleotide sequences encoding the same amino acid sequences. Also included in the invention are biologically active fragments of the protein encoded by the human cDNA of clone 188-28-4-0-B12-CS and polynucleotide sequences encoding these biologically active fragments. "Biologically active fragments" are defined as those peptide or polypeptide fragments having at least one of the biological functions of the full length protein (e.g., the ability to transform cell lines in vitro.).

The invention also provides variants of the protein of SEQ ID NO: 311, encoded by clone 188-28-4-0-B12-CS. These variants have at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the amino acid sequence encoded by clone 188-28-4-0-B12-CS. Variants according to the subject invention also have at least one functional or structural characteristic of the protein encoded by clone 188-28-4-0-B12-CS. The invention also provides biologically active fragments of the variant proteins. Unless otherwise indicated, the methods disclosed herein can be practiced utilizing the protein encoded by clone 188-28-4-0-B12-CS, or clone 188-28-4-0-B12-CS, or variants thereof. Likewise, the methods of the subject invention can be practiced using biologically active fragments of the protein encoded by clone 188-28-4-0-B12-CS, clone 188-28-4-0-B12-CS, or variants of said biologically active fragments.

Because of the redundancy of the genetic code, a variety of different DNA sequences can encode the amino acid sequence provided by clone 188-28-4-0-B12-CS. It is well within the skill of a person trained in the art to create these alternative DNA sequences encoding proteins having the same, or essentially the same, amino acid sequence. These variant DNA sequences are, thus, within the scope of the subject invention. As used herein, reference to "essentially the same" sequence refers to sequences that have amino acid substitutions, deletions, additions, or insertions that do not materially affect biological activity. Fragments retaining one or more characteristic biological activity of the protein encoded by clone 188-28-4-0-B12-CS are also included in this definition.

"Recombinant nucleotide variants" are alternate polynucleotides which encode a particular protein. They can be synthesized, for example, by making use of the "redundancy" in the genetic code. Various codon substitutions, such as the silent changes which produce specific restriction sites or codon usage-specific mutations, can be introduced to optimize cloning into a plasmid or viral vector or expression in a particular prokaryotic or eukaryotic host system, respectively.

It is believed that the protein of SEQ ID NO: 406 or part thereof plays a role in the control of gene expression, probably as a transcription repressor. The protein of the invention is thought to be able to bind to other proteins, preferably to nuclear proteins, more preferably to Rb. Preferred polypeptides of the invention are polypeptides comprising fragments of SEQ ID NO: 406 from position 159-373, 267-304 and 333-370. Other preferred polypeptides of the invention are polypeptides comprising fragments of SEQ ID NO: 406 having any of the biological activity described herein. The ability of the protein of the invention or part thereof to function as a transcription repressor may be assessed using techniques well known to those skilled in the art including those described previously (Weintraub SJ (1995) Nature 375:812-815; Qian YW (1995) J.Biol.Chem. 270:25507-25513). The ability of the protein of the invention or part thereof, especially fragments containing WD-repeats, to bind to other proteins may be assessed using techniques well known to those skilled in the art including those described herein. For example, the protein of the invention could be used as a "bait" protein in a yeast double hybridization system (e.g. Gal-4-based system from Clontech) to isolate and eventually to identify its interacting protein partner in vivo from a cDNA library. Alternatively, the protein of the invention or part thereof can be used either in a pure form or in a fusion form (linked to a reporter gene product, such as alkaline phosphatase) to screen a phage cDNA expression library derived from selected tissues or cell types of a given organism (Scott et al (1990) Science 249:386-390; Lam et al (1992) Nature 354:82-84). Preferably, the binding ability of protein of the invention is tested in mammalian cell transfection experiments. When fused in-frame to a suitable peptide tag in expression vector, such as $[His]_6$ in the pRset expression plasmid vector (Invitrogen) and introduced into culture cells, the proteins that bind to the expressed fusion protein can be immunoprecipitated using anti-$[His]_6$ antibody. This approach can also be employed to confirm the findings obtained from either yeast double hybridization system or in vitro phage peptide library screening. In this case, the putative interacting partner protein will be fused to a distinct tag in a second expression vector and co-transfected into culture cells. True binding complex will be co-immunoprecipitated with the two different anti-tag antibodies. In a particular embodiment, an affinity chromatography method is carried out to identify the interacting protein partners in vitro from cell lysates as performed for the identification of the RbAp48 protein (Qian YW et al. (1993) Nature 364:648-652).

An embodiment of the present invention relates to methods of using the protein of the invention or part thereof, particularly polypeptides containing WD-motifs, or derivative thereof to identify and/or quantify binding proteins, preferably nuclear proteins, more preferably Rb, in a biological sample, and thus used in assays and diagnostic kits for the quantification of such binding proteins in bodily fluids, in tissue samples, and in mammalian cell cultures. Such assays may be particularly useful as diagnostic or prognostic tools in the detection and monitoring of a disorder linked to dysregulation of expression of a transcription regulator. Such assays may thus be very useful to asses the level of the tumor suppressor Rb in disorders including but not limited to developmental disorders, cancers such as retinoblastoma, prostate carcinoma, osteosarcoma, breast

components of the epithelial paracellular permeability barrier. TJ breakdown nonspecifically increases epithelial permeability, allowing Der p1 to cross the epithelial barrier. Putative Der p1 cleavage sites were found in peptides from an extracellular domain of claudin. HDM allergens are important factors in the increasing prevalence of asthma (Wan H et al. J Clin Invest 104(1):123-33 (1999) which disclosure is hereby incorporated by reference in its entirety).

In a preferred embodiment, the present invention provides for a method to use the proteins of SEQ ID NOs: 391 and 407 for in vitro analysis of claudin-8 function. Further preferred is a method of using the proteins of SEQ ID NOs: 391 and 407 for in vitro analysis of the impaired claudin-8 function of said proteins. Further preferred is a method of in vitro analysis of signaling function of the protein of SEQ ID NO: 407. Further preferred is a method of in vitro analysis of signaling function of the protein of SEQ ID NO: 407 as it relates to the activation or differentiation of non-epithelial cells. Further preferred is a method of in vitro analysis of signaling function of the protein of SEQ ID NO: 407 as it relates to the activation or differentiation of leukocytes, keratinocytes, and endothelial cells.

In a preferred embodiment, the present invention provides for a method to determine the expression of the novel claudin-8 isoforms corresponding to the proteins of SEQ ID NOs: 391 and 407. Further preferred is a method of determining expression of the proteins of SEQ ID NOs: 391 and 407 as it relates to the profiling (for purposes of diagnosis or classification) of pathologies. Further preferred is a method of determining expression of the proteins of SEQ ID NOs: 391 and 407 as it relates to the profiling of Crohn's disease, ulcerative colitis, irritable bowel syndrome, allergic asthma, gliobastoma, colorectal carcinoma, and adenomatous polyps. Further preferred is a method of using nucleic acid sequence corresponding to the proteins of SEQ ID NOs: 391 and 407, namely that comprising SEQ ID Nos: 150 and 166 respectively, to determine the expression of the proteins of SEQ ID NOs: 391 and 407 in said pathologies. Further preferred is a method wherein reverse transcription-polymerase chain reaction (RT-PCR) is used in said method to determine the expression of the proteins of SEQ ID NOs: 391 and 407 in said pathologies. The methods of design of such RT-PCR analysis are known by those skilled in the art.

In a preferred embodiment, the present invention provides for a method in which the proteins of SEQ ID Nos: 391, 393, 405 and 407, or biologically active fragments thereof, are used to treat asthma or reduce the incidence of asthmatic attacks. Further preferred are compositions comprised of the proteins of SEQ ID Nos: 391, 393, 405 and 407, or biologically active fragments thereof. Further preferred are formulation of said compositions that are compatible with therapeutic administration as an aerosol. Further preferred is a method wherein purified fragments or synthetically modified peptides derived from the extracellular domains of the proteins of SEQ ID Nos: 391, 393, 405 and 407 are administered in the said therapeutic regimen. Further preferred embodiment is a method of using said peptides wherein the peptides contain the putative cleavage sites for environmental allergen proteinases and wherein said peptides are administrated in amounts that competitively inhibit the proteinase activity of the allergen.

including diabetes insipidus (vasopressin), hyper- and hypoglycemia (insulin, glucagon), Grave's disease and goiter (thyroid hormone), and Cushing's and Addison's diseases (adrenocorticotropic hormone; ACTH).

Further, cancer cells secrete excessive amounts of hormones or other biologically active peptides. Disorders related to excessive secretion of biologically active peptides by tumor cells include: fasting hypoglycemia due to increased insulin secretion from insulinoma-islet cell tumors; hypertension due to increased epinephrine and norepinephrine secreted from pheochromocytomas of the adrenal medulla and sympathetic paraganglia; and carcinoid syndrome, which includes abdominal cramps, diarrhea, and valvular heart disease, caused by excessive amounts of vasoactive substances (serotonin, bradykinin, histamine, prostaglandins, and polypeptide hormones) secreted from intestinal tumors. Ectopic synthesis and secretion of biologically active peptides (peptides not expected from a tumor) includes ACTH and vasopressin in lung and pancreatic cancers; parathyroid hormone in lung and bladder cancers; calcitonin in lung and breast cancers; and thyroid-stimulating hormone in medullary thyroid carcinoma.

It is believed that the protein of SEQ ID NO:419 or part thereof is an integral membrane protein of the SNARE-related family, and more presumably is the human homologue of the yeast SFT2p protein. Thus, the protein of the invention plays a role in the secretory and endocytic pathway of eukaryotic cells through fusion and transport of vesicles from the endoplasmic reticulum to late Golgi cisternae. Preferred polypeptides of the invention are polypeptides comprising the amino acids of SEQ ID NO:419 of the four transmembrane domains from positions 36 to 56, 66 to 86, 98 to 118 and 122 to 142. Other preferred polypeptides of the invention are fragments of SEQ ID NO:419 having any of the biological activities described herein.

In one embodiment, the invention relates to methods and compositions using the protein of the invention or part thereof as a new marker protein to selectively identify secretory and endocytic traffic, preferably in the endoplasmic reticulum and more preferably in the late Golgi cisternae. For example, the protein of the invention or part thereof may be detected using specific antibodies generated against the protein using any technique known to those skilled in the art. Such organelle-specific antibodies may then be used to identify cells with disrupted trafficking systems such as in differentiated tumor cells or to differentiate specific organelle types in a cell cross-section using immunochemistry. In addition, the protein of the invention can be used to specifically identify cells of the brain and/or placenta, tissues in which the protein is overexpressed.

Another embodiment of the present invention relates to methods of targeting heterologous compounds, such as polypeptides or polynucleotides, to the endoplasmic reticulum and preferentially to late Golgi vesicles by recombinantly or chemically fusing a fragment of the protein of the invention to the heterologous polypeptide or polynucleotide. Such fusion proteins may be engineered to contain a cleavage site located between a sequence encoding the protein of the invention and the heterologous protein sequence, so that the protein of the invention may be cleaved and purified away from the

30, 35, 40, 50, 60, 75, 100, 150, or 200 consecutive amino acids thereof, are used to treat immune disorders. This method comprises the step of administering pENK16 polypeptide or fragments thereof directly to the individual or, alternatively, administering a polynucleotide cassette comprising polynucleotides encoding said polypeptides by methods common to the art including those included herein. Alternatively, an agent which increases the activity of endogenous pENK16 polypeptides or fragments thereof is administered to the individual.

In another embodiment of the present invention, pENK16 polypeptides or fragments thereof are used to make antibodies. These antibodies may be used in methods to inhibit pENK16 activity, for example, by interfering with receptor binding, or to detect pENK polypeptides or fragments thereof, for example, to diagnose disorders associated with altered expression of pENK16. In a further embodiment of the invention, antibodies that bind pENK16 polypeptides or fragments thereof are used to detect said polypeptides in an individual using techniques common to the art such as fluorescent labeling of the antibody. The level of pENK16 polypeptides or fragments thereof in the individual may be compared to the level in normal individuals to determine whether the individual has an abnormal level of pENK16 polypeptides associated with disease.

Enkephalins also have anti-bacterial activity. pENK16 protein processing involves removal of the carboxy-terminal end. Further processing results in a bisphosphorylated peptide of about 30 amino acids (ENK16BPP) which possesses antibacterial activity against gram-positive bacteria such as *Staphylococcus aureus, Micrococcus luteus* and *Bacillus megaterium* (0.2-0.4 μM range). ENK16BPP is present in wound fluids along with other known antibacterial peptides (defensins, bactenecins). The concentrations were in a range similar to that found to be active *in vitro* (0.5-1 μM). ENK16BPP is detected in secretions from human polymorphonuclear neutrophils and cultured chromaffin cells following stimulation. Co-release of met-enkephalin and ENK16BPP represent a unified neuroimmune protective response to stress situations and infectious diseases providing a beneficial survival strategy at the begninning of proinflammatory processes. pENK16 therefore plays an important role in host defense against microbial infections, especially those involving gram positive bacteria, inflammatory processes, and wound repair. In a preferred embodiment of the invention, an antibiotic effective amount of pENK16 polypeptides and fragments thereof are used to prevent microbial infection. Preferred pENK16 fragments include ENK16BPP. This method comprises the step of contacting pENK16 polypeptides or fragments thereof in a physiologically acceptable solution (e.g., pH-buffered saline) with areas of microbial infection or possible microbial infection, including wounds and incisions. Further methods include using pENK16 or fragments thereof as antibacterial agents in creams/ointments/solutions, presoaked bandages, or dermal-type patches for external applications. Alternatively, pENK16 polypeptides or fragments thereof may be used in injections (intravenously, subcutaneously or intra-peritoneally). This is useful for wound repair, burn healing, post-operative recovery management. Alternatively, pENK16 polypeptides or

PCP-2 contains three membrane-spanning segments located between amino acid positions 6 and 26, 73 and 93, or 139 and 159 and a signal peptide comprising the sequence FAAFCYMLSLVLC/AA. Accordingly, one embodiment of the present invention is a polypeptide comprising one or more of the membrane-spanning segments, and/or the signal peptide. PCP-2 is a member of the cornichon protein family.

PCP-2 polypeptides are expressed in activated T-cells, T cell helper II cells, granulocytic cells, monocytic cells, Raji cells treated with cyclohexamide, and CD34+ hematopoetic stem cells. This expression pattern indicates that PCP-2 polypeptides play a role in regulating the proliferation, survival, differentiation, and activation of hematopoetic cells. Furthermore, PCP-2 polypeptide is involved in regulation of cytokine and growth factor production and processing, suggesting a mechanism for these activities. In a preferred embodiment of the invention, PCP-2 polypeptides, fragments thereof, or polynucleotides encoding said polypeptides are used to increase cytokine/ growth factor secretion. Preferred cytokines are members of the Epithelial Growth Factor (EGF) and Transforming Growth Factor (TGF) families, in particular, EGF and TGF-α. This method comprises the step of introducing PCP-2 polypeptides to a cell. Preferred cells are those that secrete cytokines. Further preferred cells are those that secrete EGF or TGF-α. A preferred method of introducing PCP-2 polypeptides to a cell includes introducing a polynucleotide construct comprising polynucleotides encoding a PCP-2 polypeptide to said cell by methods common to the art such as transfection or electroporation. Further methods of polynucleotide introduction include but are not limited to: lipid vesicle delivery (including micelles, viral envelope components, lipsomes, and modified versions of these) as discussed in U.S. Patent 6110490, U.S. Patent 5019369, and P.C.T. 9704748, which disclosures are hereby incorporated by reference in their entireties and viral transduction (including attenuated lentiviral and adenoviral systems) as discussed in U.S. Patent 6204060, which disclosure is hereby incorporated by reference in its entirety.

In another embodiment of the invention, PCP-2 polypeptides, fragments thereof, or polynucleotides encoding said polypeptides are introduced into autologous cells obtained from an individual for the purpose of reintroducing cytokine-producing cells. This method is directed toward treatment of cytokine-deficiency disorders. Preferred cells include cells capable of producing cytokines, in particular T cells. Introduction of PCP-2 polypeptides or polynucleotides is accomplished by methods common to the art, such as those discussed above. After introduction of said polypeptides or polynucleotides, cells are expanded and reintroduced into the individual from which the cells were obtained (U.S. Patent Nos. 5,192,537 and 5,766,920, which disclosures are hereby incorporated by reference in their entireties).

In another embodiment of the subject invention, PCP-2 polypeptides, fragments thereof, and polynucleotides encoding said polypeptides are used to expand stem cells, committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell

covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

In another embodiment, the protein of SEQ ID NO:283 or 286 or a fragment or derivative thereof may be administered to a subject to diagnose, treat or prevent an immune disorder associated with decreased expression or activity of the protein of the invention. Such disorders can include, but are not limited to, acquired immunodeficiency syndrome (AIDS), X-linked agammaglobinemia of Bruton, common variable immunodeficiency (CVI), DiGeorge's syndrome (thymic hypoplasia), thymic dysplasia, isolated IgA deficiency, severe combined immunodeficiency disease (SCID), immunodeficiency with thrombocytopenia and eczema (Wiskott-Aldrich syndrome), Chediak-Higashi syndrome, chronic granulomatous diseases, hereditary angioneurotic edema, immunodeficiency associated with Cushing's disease, Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjogren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, leukemias such as multiple myeloma, and lymphomas such as Hodgkin's disease. In addition, such disorders associated with decreased protein expression or activity can be treated by administering to a patient polynucleotide sequences encoding the protein of the invention, e.g. inserted in an appropriate vector. In another example, a compound that increases either the activity of the protein of the invention or their expression can be administered to a patient to treat or prevent any of the diseases mentioned above.

In a further embodiment, an antagonist of the protein of the invention may be administered to a subject to treat or prevent an immune disorder associated with increased expression or activity of the protein of SEQ ID NO:283 or 286 including, but not limited to, auto-immune deseases or graft rejection. In one aspect, an antibody which specifically binds the protein of the invention may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express the proteins of the invention, such as the salivary gland tissue or the bone marrow tissue. In addition, sense, antisense nucleotides, GSE, ribozymes, specific protein inhibitors such as antibodies or small coumpounds can be administered to inhibit the expression of the proteins of the invention.

In another embodiment, an antagonist of the protein of SEQ ID NO:283 may be administered to a subject to treat or prevent a cell proliferative disorder. Such disorders may include, but are not

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Indeed, the 80 first amino-acids of the protein of the invention are identical to two polypeptides claimed in Patent WO 99/35158, hereby incorporated by reference in its entirety (SEQ ID NO:98 and SEQ ID NO:162 corresponding to Geneseq accession numbers Y38413/Y38428 and Y38492) are over-expressed in pulmonary and endothelial tissues.

The tissue distribution in pulmonary and endothelial tissues indicates that the protein product described in WO 99/35158 is useful for the treatment and diagnosis of cardiovascular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stroke, angina, thrombosis hypertension, inflammation, and wound healing. Those conditions can be diagnosed by determining the amount of the protein of the invention in a sample. Thus, antibodies raised against the protein of SEQ ID NO: 287, or an immunogenic fragment of the protein can be used in diagnostic, prognostic, or screening assays such as those taught in WO 99/35158.

Protein of SEQ ID No. 270 (internal designation 116-119-3-0-H5-CS)

The protein of SEQ ID NO: 270 encoded by the extended cDNA SEQ ID NO: 29 is homologous to the human mitochondrial ATP synthase f subunit or ATPK (E.C. 3.6.1.34) (Swissprot accession number P56134) and is overexpressed in fetal kidney.

The protein of SEQ ID NO: 270, composed of 88 amino acid residues, contains 1 transmembrane segment (position 1 to 55) predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10 :685-686 (1994). BLAST results show that 100% homology is found between amino acids 5 to 88 of the protein of the invention and amino acids 10 to 93 of human ATP synthase f chain (93 amino acids total), exon 1 of the cDNA SEQ ID NO: 29 making the difference between the 2 proteins (the last 3 exons show 100% homology). Thus, the protein of the invention represents a new isoform of human mitochondrial ATP synthase f subunit. It is interesting to note that the same splice variant is found in bovin, pig and mouse species.

The mitochondrial electron transport (or respiratory) chain is a series of enzyme complexes in the mitochondrial membrane that is responsible for the transport of electrons from NADH to oxygen and the coupling of this oxidation to the synthesis of ATP (oxidative phosphorylation). ATP then provides the primary source of energy for driving a cell's many energy-requiring reactions. ATP synthase (F0 F1 ATPase) is the enzyme complex at the terminus of this chain and serves as a reversible coupling device that interconverts the energies of an electrochemical proton gradient across the mitochondrial membrane into either the synthesis or hydrolysis of ATP. This gradient is produced by other enzymes of the respiratory chain in the course of electron transport from NADH to oxygen. When the cell's energy demands are high, electron transport from NADH to oxygen generates an electrochemical gradient across the mitochondrial membrane. Proton translocation from the outer to the inner side of the membrane drives the synthesis of ATP. Under conditions of low energy requirements and when there is an excess of

may be a hard disk, a floppy disk, a magnetic tape, CD-ROM, Digital Versatile Disk (DVD), Random Access Memory (RAM), or Read Only Memory (ROM) as well as other types of other media known to those skilled in the art.

Embodiments of the present invention include systems, particularly computer systems which store and manipulate the sequence information described herein. One example of a computer system 100 is illustrated in block diagram form in Figure 2. As used herein, "a computer system" refers to the hardware components, software components, and data storage components used to analyze the nucleotide sequences of the nucleic acid codes of the invention or the amino acid sequences of the polypeptide codes of the invention. In one embodiment, the computer system 100 is a Sun Enterprise 1000 server (Sun Microsystems, Palo Alto, CA). The computer system 100 preferably includes a processor for processing, accessing and manipulating the sequence data. The processor 105 can be any well-known type of central processing unit, such as the Pentium III from Intel Corporation, or similar processor from Sun, Motorola, Compaq or International Business Machines.

Preferably, the computer system 100 is a general purpose system that comprises the processor 105 and one or more internal data storage components 110 for storing data, and one or more data retrieving devices for retrieving the data stored on the data storage components. A skilled artisan can readily appreciate that any one of the currently available computer systems are suitable.

In one particular embodiment, the computer system 100 includes a processor 105 connected to a bus which is connected to a main memory 115 (preferably implemented as RAM) and one or more internal data storage devices 110, such as a hard drive and/or other computer readable media having data recorded thereon. In some embodiments, the computer system 100 further includes one or more data retrieving device 118 for reading the data stored on the internal data storage devices 110.

The data retrieving device 118 may represent, for example, a floppy disk drive, a compact disk drive, a magnetic tape drive, etc. In some embodiments, the internal data storage device 110 is a removable computer readable medium such as a floppy disk, a compact disk, a magnetic tape, etc. containing control logic and/or data recorded thereon. The computer system 100 may advantageously include or be programmed by appropriate software for reading the control logic and/or the data from the data storage component once inserted in the data retrieving device.

The computer system 100 includes a display 120 which is used to display output to a computer user. It should also be noted that the computer system 100 can be linked to other computer systems 125a-c in a network or wide area network to provide centralized access to the computer system 100.

Software for accessing and processing the nucleotide sequences of the nucleic acid codes of the invention or the amino acid sequences of the polypeptide codes of the invention (such as search tools, compare tools, and modeling tools etc.) may reside in main memory 115 during execution.

In some embodiments, the computer system 100 may further comprise a sequence comparer for comparing the above-described nucleic acid codes of the invention or the polypeptide codes of the

779, 1986; Mason *et al.*, *Nature* 318:659-663, 1985; Forage *et al.*, *Proc. Natl. Acad. Sci. USA* 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan *et al.* Eds. Greene Publishing Associates and Wiley-Intersciece ; Taub *et al. J. Clin. Invest.* 95:1370-1376, 1995; Lind *et al. APMIS* 103:140-146, 1995; Muller *et al. Eur. J. Immunol.* 25:1744-1748; Gruber *et al. J. of Immunol.* 152:5860-5867, 1994; Johnston *et al. J. of Immunol.* 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885, the disclosure of which is incorporated herein by reference. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

Assaying GENSET proteins or Fragments Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the cDNAs of the invention or fragments thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

162	[1-505];[575-759];[761-1164]	[506-574];[760-760];[1165-1176]
163	[1-699]	[700-1084]
164	[38-483];[485-556]	[1-37];[484-484];[557-1793]
165	[1-426];[1303-1444];[1717-1755];[1787-1825]	[427-1302];[1445-1716];[1756-1786];[1826-1849]
166	[2-264];[266-446];[448-519]	[1-1];[265-265];[447-447];[520-1748]
167	[1-519];[523-552]	[520-522];[553-1275]
168	[1-457];[466-571]	[458-465];[572-1023]
169	[1-54];[57-501]	[55-56];[502-1085]
170	[1-541]	[542-776]
171	[1-489]	[490-1219]
172	[1-538];[977-1468]	[539-976];[1469-1487]
173	[1-631]	[632-1915]
174	[21-776];[888-967];[969-1061];[1063-1137];[1819-1967]	[1-20];[777-887];[968-968];[1062-1062];[1138-1818];[1968-1990]
175	[1-508]	[509-1971]
176	[1-127];[129-538];[979-1470]	[128-128];[539-978];[1471-1613]
177	[1-535];[973-1173];[1177-1330];[1332-1361]	[536-972];[1174-1176];[1331-1331]
178	[1-599];[626-830];[1082-1113]	[600-625];[831-1081]
179	[1-623];[1377-1406]	[624-1376];[1407-1960]
180	[1-414];[418-464]	[415-417];[465-1443]
181	[1-522];[533-587]	[523-532];[588-605]
182	[1-78];[99-131];[136-327];[1153-1184];[1210-1274];[1284-1319];[1385-1416]	[79-98];[132-135];[328-1152];[1185-1209];[1275-1283];[1320-1384];[1417-1724]
183	[1-512];[617-805];[871-952];[1387-1422];[1621-1661]	[513-616];[806-870];[953-1386];[1423-1620];[1662-1686]
184	[1-453]	[454-463]
185	[1-773]	None
186	[1-413];[423-604];[606-739]	[414-422];[605-605];[740-753]
187	[1-117];[119-401]	[118-118];[402-754]
188	[1-511];[684-870];[872-928];[935-981]	[512-683];[871-871];[929-934];[982-998]
189	[1-605]	None
190	[2-475]	[1-1];[476-526]
191	[1-910]	None
192	[1-101];[103-668]	[102-102]
193	[1-520];[583-637]	[521-582]
194	[1-706]	None
195	[1-145];[150-451];[466-670]	[146-149];[452-465]
196	[1-509]	[510-510]
197	[1-500]	None
198	[1-503];[505-585]	[504-504];[586-667]
199	[1-498]	[499-514]
200	[1-462]	None
201	[1-551]	None
202	[1-482];[484-550]	[483-483]
203	[1-408]	None

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2,
Line 2, "ofter" should read --often--.

Column 12,
Line 61, "60/187" should read --60/187,470--.

Column 16,
Line 19, "96%, 96%, 98relative to" should read --96%, 96%, 98%, 99%, or 100% pure relative to--.

Column 22,
Line 18, "Randomization Group25" should read --Randomization Group 25,--.

Column 32,
Line 61, "present invention is a" should read --present invention are a--.

Column 35,
Line 29, "telomerc repeats" should read --telomeric repeats--.

Column 43,
Line 18, "either fill-length" should read --either full-length--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 63,
Lines 35-36, "$5x10^{-}{}_{15}M$" should read --$5x10^{-15}M$--.

Column 83,
Line 36, "containing 25 ∞g/ml" should read --containing 25 μg/ml--.

Column 86,
Line 26, "between 0,1 and" should read --between 0.1 and--.

Column 95,
Line 37, "groups firm" should read --groups from--.

Column 99,
Line 19, "contain domain" should read --contain the LRR domain--.

Column 102,
Line 9, "chromatograpy" should read --chromatography--.

Column 103,
Line 5, "binding domain domain" should read --binding domain--.
Line 24, "zinc fingers domains" should read --zinc finger domains--.

Column 107,
Line 49, "shown to activates" should read --shown to activate--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 108,
Line 10, "exemple" should read --example--.
Line 44, "immunohistochemisty" should read --immunohistochemistry--.

Column 110,
Line 58, "extramacrochactac" should read --extramacrochaetae--.

Column 113,
Line 55, "invention havinf an" should read --invention having an--.

Column 127,
Lines 31-32, "is caracterized by" should read --is characterized by--.
Line 52, "plant epoxyde hydrolase" should read --plant epoxide hydrolase--.
Line 58, "hydratation" should read --hydration--.

Column 128,
Line 11, "may be associed with" should read --may be associated with--.
Line 35, "an epoxyde hydrolase" should read --an epoxide hydrolase--.

Column 129,
Line 29, "Biochemistry 29 1425-1435" should read --Biochemistry 29:1425-1435--.
Line 60, "nutrient and gaz" should read --nutrient and gas--.

Column 130,
Line 26, "deficient fonction" should read --deficient function--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 131,
Line 38, "that is the hallmarks" should read --that is the hallmark--.

Column 132,
Line 17, "participate to regulation" should read --participate in regulation--.

Column 133,
Line 51, "immunohistochemisty" should read --immunohistochemistry--.

Column 136,
Lines 65-66, "and embryogenesis Individuals" should read --and embryogenesis. Individuals--.

Column 140,
Line 54, "alkali bums" should read --alkali burns--.

Column 143,
Line 10, "treatment of bums" should read --treatment of burns--.
Line 13, "healing of bums. The bums" should read --healing of burns. The burns--.
Line 17, "there are bums" should read --there are burns--.
Line 18, "contacting the bum" should read --contacting the burn--.

Column 146,
Line 25, "thuman pancreatic" should read --human pancreatic--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 149,
Lines 36-37, "Kaun et Saier," should read --Kaun and Saier--.

Column 150,
Line 4, "Kaun et Saier" should read --Kaun and Saider--.

Column 153,
Lines 34-35, "composition and methods" should read --compositions and methods--.

Column 155,
Line 32, "donnor" should read --donor--.

Column 156,
Line 37, "celullar proteins" should read --cellular proteins--.

Column 157,
Line 62, "fusosyltransferase" should read --fucosyltransferase--.

Column 159,
Line 5, "model of" should read --models of--.
Line 11, "fusosyltransferase" should read --fucosyltransferase--.
Line 21, "or pat thereof" should read --or part thereof--.
Line 55, "related to" should read --relates to--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 160,
Line 47, "immunohistochemisty" should read --immunohistochemistry--.

Column 164,
Line 15, "framents thereof" should read --fragments thereof--.

Column 168,
Line 15, "chromatograpy" should read --"chromatography--

Column 173,
Line 12, "exemple" should read --example--.
Line 23, "exemple" should read --example--.

Column 174,
Line 36, "relulation" should read --regulation--.

Column 177,
Line 16, "immunohistochemisty" should read --immunohistochemistry--.
Line 29, "U.S. Pat. No. 552,277" should read --U.S. Pat. No. 5,552,277--.

Column 186,
Line 30, "$p34^{SEI-}$ seems" should read --$p34^{SEI-1}$ seems--.

Column 191,
Line 6, "purified the protein" should read --purified protein--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 192,
Line 51, "SEQ ID NO: HOPP" should read --SEQ ID NO: 259--.

Column 193,
Line 37, "methods Kohler" should read --methods of Kohler--.

Column 195,
Line 27, "clone 15 188-28-4-0-B12-CS" should read --clone 188-28-4-0-B12-CS--.

Column 198,
Line 59, "to functions as" should read --to function as--.

Column 201,
Line 8, "conserved cysteines residues" should read --conserved cysteine residues--.

Column 206,
Line 66, "memebers" should read --members--.

Column 209,
Lines 31-32, "metastatispreferably brain cancer" should read --metastasis, preferably brain cancer--.

Column 211,
Line 21, "trought its" should read --through its--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 212,
Line 49, "eucaryote" should read --eukaryote--.
Line 54, "procaryote" should read --prokaryote--.

Column 213,
Line 42, "neuromuscularjunction" should read --neuromuscular junction--.

Column 217,
Line 29, "marquer" should read --marker--.
Line 52, "postherpetic" should read --post-therapeutic--.

Column 223,
Line 31, "gliobastoma" should read --glioblastoma--.
Line 48, "fragments thereof Further preferred" should read --fragments thereof. Further preferred--.

Column 224,
Line 37, "In further" should read --In a further--.

Column 225,
Line 1, "in further" should read --in a further--.
Line 19, "In further" should read --In a further--.

Column 226,
Line 6, "gliobastoma" should read --glioblastoma--.
Line 19, "gliobastoma" should read --glioblastoma--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 234,
Lines 17-18, "Golgi cistemae" should read --Golgi cisternae--.

Column 237,
Line 62, "gliobastoma" should read --glioblastoma--.

Column 239,
Line 1, "In further" should read --In a further--.
Line 32, "in further" should read --in a further--.
Line 50, "In further" should read --In a further--.

Column 240,
Line 37, "gliobastoma" should read --glioblastoma--.
Line 50, "gliobastoma" should read --glioblastoma--.

Column 241,
Line 49, "neurogenerative" should read --neurodegenerative--.
Line 60, "provide methods" should read --provides methods--.

Column 242,
Lines 15-16, "neurogenerative" should read --neurodegenerative--.
Lines 64-65, "neurogenerative" should read --neurodegenerative--.

Column 244,
Line 61, "int the" should read --in the--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 246,
Line 3, "Cterminal" should read --C terminal--.

Column 249,
Line 10, "Pancreas :139-149" should read --Pancreas 9(2):139-149--.

Column 251,
Line 4, "chromatograpy" should read --chromatography--.
Line 4, "prepartation" should read --preparation--.
Line 57, "(1993" should read --(1993)--.

Column 257,
Line 66, "In further" should read --In a further--.

Column 258,
Line 9, "In further" should read --In a further--.
Line 23, "In further" should read --In a further--.

Column 260,
Line 6, "In further" should read --In a further--.
Line 9, "In further" should read --In a further--.

Column 263,
Line 4, "diarrhoea" should read --diarrhea--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479
APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 265,
Line 15, "CO2 hydration" should read --CO_2 hydration--.
Line 26, "CO2 hydration" should read --CO_2 hydration--.

Column 267,
Line 53, "chromatograpy" should read --chromatography--.

Column 268,
Line 52, "doamins" should read --domains--.

Column 275,
Line 4, "frombrain" should read --from brain--.
Line 28, "chromatograpy" should read --chromatography--.

Column 281,
Line 22, "chromatograpy" should read --chromatography--.
Line 23, "prepartation" should read --preparation--.
Line 65, "exon2" should read --exon 2--.

Column 282,
Line 3, "intron1" should read --intron 1--.
Line 20, "differenctiation" should read --differentiation--.
Line 44, "Some throughly studied" should read --Some thoroughly studied--.
Line 47, "et Al reported" should read --et al. reported--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 283,
Line 61, "chromatograpy" should read --chromatography--.
Line 61, "prepartation" should read --preparation--.

Column 292,
Line 29, " bum healing" should read -- burn healing--.

Column 293,
Line 21, "polypeptidehas" should read --polypeptide has--.

Column 294,
Line 63, "demntia" should read --dementia--.

Column 295,
Line 61, "comichon" should read --cornichon--.

Column 297,
Line 32, "demntia" should read --dementia--.

Column 300,
Line 26, "twomembrane-spanning" should read --two membrane-spanning--.

Column 303,
Line 41, "particulary" should read --particularly--.

Column 304,
Line 61, "svere" should read --severe--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 309,
Line 34, "Croh's disease" should read --Crohn's disease--.

Column 314,
Line 45, "enzymes labels" should read --enzyme labels--.

Column 322,
Line 10, "Protiens of" should read --Protein of--.

Column 324,
Line 12, "embodiment, The" should read --embodiment, the--.

Column 336,
Line 4, "specifically bine the" should read --specifically bind the--.

Column 342,
Line 48, "potasssium" should read --potassium--.

Column 347,
Line 66, "specifically binds a" should read --specifically bind a--.

Column 351,
Line 25, "compartments/organelels" should read --compartments/organelles--.

Column 353,
Line 28, "(e.g. biopsies." should read --(e.g. biopsies).--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,060,479

APPLICATION NO.: 09/876,997

DATED : June 13, 2006

INVENTOR : Jean-Baptiste Dumas Milne Edwards, Lydie Bougueleret, Severin Jobert

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 355,
Line 13, "Diphteria toxin A" should read --Diphtheria toxin A--.

Column 367,
Line 12, "biological activty" should read --biological activity--.

Column 372,
Line 35, "titaniumdioxide" should read --titanium dioxide--.

Column 376,
Line 2, "manipule" should read --manipulate--.

Column 394,
Lines 47-48, "Muller et al. I Eur. J." should read --Muller et al. Eur. J.--.

Column 433,
Table Vb, SEQ ID NO: 166, "1-1];" should read --[1-1];--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950